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Otto, Sijbren; Engberts, Jan B.F.N.

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Diels–Alder reactions in water*

Sijbren Otto and Jan B. F. N. Engberts

*Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute,
University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands*

Abstract: This review illustrates how water, as an environmentally friendly solvent, can have significant additional benefits when it is used as a solvent for the Diels–Alder reaction. The mechanism by which the unique properties of water enhance the rate and selectivity are discussed. Also, possibilities for the achievement of further increases in rate and enantioselectivity of aqueous Diels–Alder reactions through Lewis-acid and micellar catalysis are reviewed.

INTRODUCTION

An important part of our efforts towards a more environmentally friendly, green chemistry is aimed at a reduction of the use of organic solvents. Usually, organic solvents are used in much larger quantities than the solutes they carry and have a tendency to escape into the environment through evaporation and leakage. A lot of research is currently devoted to the replacement of organic solvents by a less environmentally hazardous one. Nature's own solvent, water, is ideally suited for this purpose owing to its non-toxic character. Its enormous abundance on this planet makes water a cheap and readily accessible alternative.

The increased focus on water in synthetic organic chemistry during the past few decades has resulted in a large number of reactions that can now be performed successfully in an aqueous medium. Among these reactions are allylation reactions, the aldol condensation, the Michael addition, the Mannich reaction, indium-mediated allylation and Grignard-type additions and the benzoin condensation [1]. Surprisingly, also notoriously solvent-insensitive reactions such as the Claisen rearrangement and the 1,3-dipolar cycloaddition can benefit dramatically from an aqueous medium. Perhaps the most striking and unexpected example of a reaction that benefits from the use of an aqueous solvent system is the Diels–Alder reaction. Herein we will summarize how the unique properties of water, as expressed in strong hydrogen bonding interactions and hydrophobic interactions, enhance the rate and selectivity of this important organic transformation. The synthetic merits of these effects will be briefly highlighted. Finally, the considerable potential of catalysis of Diels–Alder reactions in water by micellar aggregates and Lewis acids will be briefly discussed.

SPECIAL EFFECTS OF WATER ON DIELS–ALDER REACTIONS

For a long time water was not a popular solvent for the Diels–Alder reaction. Before 1980 its use had been reported only incidentally. Diels and Alder themselves performed the reaction between furan and maleic acid in an aqueous medium in 1931 [2], an experiment which was repeated by Woodward and Baer in 1948 [3]. These authors noticed a change in endo–exo selectivity when comparing the reaction in water with that in ether. Also, in two patents the Diels–Alder reaction is mentioned in connection with water [4]. In 1973 Eggelte, de Koning, and Huisman studied the reaction of maleic acid with furan in several solvents [5]. These authors noticed, for the first time, a beneficial rate effect of water on the Diels–Alder reaction. Still, it was not until the work of Breslow et al. that it became common knowledge that water was a unique medium for Diels–Alder reactions [6].

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In general, the use of an aqueous medium increases the rate of Diels–Alder reactions significantly as compared to all organic solvents. In extreme cases accelerations can exceed a factor of 10 000 [7]. In addition, aqueous solvents tend to enhance the selectivity of the reaction. More specifically, the generally observed preference for the formation of the endo cycloadduct is even more pronounced in water. Also, the regioselectivity and diastereofacial selectivity tends to increase in aqueous media.

The effect of water on the rate of Diels–Alder reactions

Breslow and Rideout [6] interpreted the acceleration of Diels–Alder reactions in water in terms of a hydrophobic effect. Alternatively, in the literature the acceleration is sometimes attributed to micellar catalysis [8]. However, since water accelerates Diels–Alder reactions also when the reactants are distributed homogeneously throughout the solution, this explanation lacks generality. Kinetic measurements on the intramolecular Diels–Alder reaction of **1** (entry 1 in Table 1) support this suggestion. In this reaction diene and dienophile are already associated, and still water is capable of accelerating this process by a factor of 153 compared to the reaction in n-hexane [9].

Studies of solvent effects on the Diels–Alder reaction led to useful insight into the origin of the special rate effect of water. Most studies have focused on type A Diels–Alder reactions [10]. A multiparameter analysis by Gajewski revealed the importance of the cohesive energy density (ced, not to be confused with the internal pressure [11]) of the solvent, together with the hydrogen-bond donating capacity [12]. The ced essentially quantifies solvophobicity, underlining the importance of hydrophobic interactions in rationalizing the effect of water on Diels–Alder reactions. This special type of hydrophobic interactions is best referred to as “enforced hydrophobic interactions” [13]. The term “enforced” is used to stress the fact that the association of the nonpolar reagents is driven by the reaction and only enhanced by water. Other solvent effect studies by a large number of authors further demonstrated that reactivity is primarily determined by two solvent parameters: the hydrogen-bond donating capacity and the solvophobicity [14]. This pattern strongly suggests that in water, a hydrogen-bond donating solvent par excellence, *the Diels–Alder reaction benefits not only from enforced hydrophobic interactions but also from hydrogen-bonding interactions*. The small size of water molecules allows efficient interaction with hydrogen-bond acceptors by forming more hydrogen bonds than protic organic solvents.

The importance of hydrogen bonding interactions is apparent from the results of detailed kinetic studies on a number of carefully selected Diels–Alder reactions. In entry 2 of Table 1 the reactions of cyclopentadiene with a carbonyl- (**3**) and a sulfonyl- (**6**) activated dienophile are compared [7a]. Due to the insulating effect of the sulfur atom in **6**, the reactivity of this compound is much less affected by hydrogen bonding than the reactivity of **3**. This decreased sensitivity of **6** to hydrogen bonding shows up in a much less pronounced water-induced acceleration as compared to that for **3**. Further support comes from a Diels–Alder reaction where the reactants lack hydrogen-bond accepting sites (entry 3) [15]. The acceleration of the reaction of **8a** with **4** by water is modest, as can be expected in the absence of activation by hydrogen bonds. However, upon introduction of a hydrogen-bond accepting substituent (**8b**) the aqueous acceleration is significantly enhanced. Finally, the reaction between cyclohexadiene and nitrosobenzene has been studied (entry 4) [16]. This reaction is classified by Desimoni as a type C Diels–Alder reaction, indicating that it is insensitive to specific interactions with the solvent, such as hydrogen bonding [10]. Consequently, the aqueous rate enhancement is modest, underlining the importance of hydrogen bonding interactions for Diels–Alder reactions that experience large beneficial effects from water.

Further insights into the peculiar features of the Diels–Alder reaction in water have been obtained from the Gibbs energies of transfer from 1-propanol to water of the starting materials and product for the Diels–Alder reaction between methyl vinyl ketone and ethyl vinyl ketone with cyclopentadiene [9]. When combined with the Gibbs energies of activation, these data allow a direct comparison of the chemical potentials of the initial states, the transition states, and the product of this reaction in these two solvents. In water the initial state is significantly destabilized relative to 1-propanol. Hydrophobic hy-

Table 1. Relative rate constants of some selected Diels–Alder reactions in water compared to organic solvents of different hydrogen-bond donor capacities.

		Aprotic	EtOH	HFP ^a	H ₂ O
1		1 (hexane)	1.90	-	153
2		1 (CH ₃ CN)	4.79	100	290
		1 (CH ₃ CN)	2.49	22.6	71.0
3		a 1 (CH ₃ CN) b -	1.69 1	- -	8.95 102
4		1 (toluene)	1.14	5.49	44.3
5		a X=NO ₂ b X=Cl c X=H d X=CH ₃ e X=OCH ₃ f X=CH ₂ SO ₃ ⁻ Na ⁺ g X=CH ₂ N ⁺ (CH ₃) ₃ Br ⁻ M=CoII, NiII, CuII, ZnII			

^a 1,1,1,3,3,3-hexafluoropropanol

dration of the initial state is clearly unfavorable compared to solvation in 1-propanol. This also applies to the product state. The transition state, however, has nearly equal chemical potentials in water and in 1-propanol. Apparently, in aqueous solution the hydrocarbon parts of the activated complex have completely lost their nonpolar character. Recent work on Diels–Alder reactions of a series of N-alkylmaleimides with different dienes has confirmed this [17]. Addition of methylene units or methyl groups to the diene results in a destabilization of the initial state of the Diels–Alder reaction with N-alkylmaleimides in water as compared to 1-propanol. Nevertheless, the transition states in water and 1-propanol have comparable chemical potentials. On the basis of computer simulations Jorgensen et al. arrived at approximately the same conclusions [18]. Recently, Furlani and Gao, following a similar approach, estimated the Gibbs energy of hydration of the Diels–Alder reaction of cyclopentadiene with isoprene and methyl vinyl ketone in water [19]. Surprisingly, the authors observed that, relative to the initial state, water stabilized the transition state of the former process more than the latter (19 kJ/mole versus 15 kJ/mole). This trend opposes the experimental data collected in Table 1, which seem to indicate that the aqueous acceleration diminishes when the hydrogen-bonding interactions become impossible.

Finally, the activation parameters for Diels–Alder reactions in water and in a number of organic solvents have been obtained. For the reaction of methyl vinyl ketone with cyclopentadiene the acceleration on going from 1,4-dioxane to water is mainly enthalpic in origin [20]. Comparing water with 1-propanol the enthalpy and entropy of activation contribute about equally [13a]. When the rate of the reaction in water is compared to that in methanol, the entropy term dominates the rate enhancement

[21]. One may conclude that hydrogen-bonding interactions mainly affect the enthalpy of activation. In contrast, under the typical reaction conditions, the hydrophobic part of the acceleration in water is most likely mainly an entropy effect. Note that the Diels–Alder reaction in water benefits from both a reduced enthalpy of activation as well as a reduced entropy of activation. This pattern is rather unusual and can be interpreted as another indication for the simultaneous operation of two mechanisms of activation.

In summary, a wealth of experimental data as well as a number of sophisticated computer simulations unequivocally indicate that *two important effects underlie the acceleration of Diels–Alder reactions in aqueous media: hydrogen bonding and enforced hydrophobic interactions*. In terms of transition state theory: hydrophobic hydration raises the initial state more than the transition state and hydrogen-bonding interactions stabilize the transition state more than the initial state. The highly polarizable activated complex plays a key role in both of these effects.

The effect of water on the selectivity of Diels–Alder reactions

Three years after the report on the large effects of water on the rate of the Diels–Alder reaction, Breslow et al. demonstrated that also the endo–exo selectivity of this reaction benefits markedly from employing aqueous media [22]. Based on the influence of salting-in and salting-out agents, Breslow pinpoints hydrophobic effects as the most important contributor to the enhanced endo–exo selectivity. Hydrophobic effects are assumed to stabilize the more compact endo transition state more than the extended exo transition state. This difference in compactness of both states is evident from the well-known smaller activation volume for the endo cycloaddition [23].

In addition, the high polarity of water is assumed to strengthen the preference for endo cycloadduct. Actually, the solvent sensitivity of the endo–exo product ratio was already recognized by Berson et al., who based an empirical solvent polarity parameter on the endo–exo ratio of the reaction between methyl acrylate and cyclopentadiene [24].

Studies of solvent effects on the endo–exo selectivity of Diels–Alder reactions have revealed the importance of hydrogen-bonding interactions besides the already mentioned solvophobic interactions and polarity effects [25]. Further evidence for the significance of the former interactions comes from computer simulations [26] and the analogy with Lewis-acid catalysis which is known to enhance dramatically the endo–exo selectivity.

In conclusion, the special influence of water on the endo–exo selectivity seems to be a result of the fact that this solvent combines in it three characteristics that all favor formation of the endo adduct: (1) water is a strong hydrogen-bond donor, (2) water is polar, and (3) water induces hydrophobic interactions.

Water is also reported to increase the diastereofacial- and regioselectivity of Diels–Alder reactions [14a,c,27]. Mechanistic investigations have been carried out on the reaction between cyclopentadiene and (1R,2S,5R)-menthyl acrylate, which has been shown to be dominated by the hydrogen-bond donor characteristics of the solvent together with its polarity [14].

Synthetic applications

Grieco was the first to demonstrate that the astonishing rate and selectivity enhancements of Diels–Alder reactions in water can be exploited successfully in organic synthesis [28]. He extensively studied the reactivity of dienes containing hydrophilic carboxylate, or ammonium groups, as well as hetero Diels–Alder reactions of iminium ions. These processes can be successfully employed in natural product synthesis.

The extensive work of Lubineau and coworkers further demonstrates the merits of water with respect to the rates and selectivities of the Diels–Alder reaction [1a,21,27a,29]. Since 1985 the Lubineau group has published a large number of articles dealing mainly with dienes that were rendered water

soluble through the temporary introduction of a sugar moiety. The efficiency of Diels–Alder reactions between these compounds and standard dienophiles is still significantly enhanced in aqueous solutions, despite the presence of the hydrophilic sugar group in the diene. The sugar moiety can be removed after completion of the Diels–Alder reaction. Lubineau et al. also studied the hetero Diels–Alder reactions of glyoxylic acid and its sodium salt in some detail. Also these reactions were shown to benefit considerably from the use of water as a solvent.

Waldmann et al. studied the possible influence of α -amino-acid derivatives as chiral auxiliaries on the diastereoselectivity of several Diels–Alder reactions in aqueous media [30]. In contrast to the advantageous influence of the medium on rate and endo–exo selectivity, Waldmann did not observe an increase in diastereofacial selectivity.

Many other authors successfully employed aqueous Diels–Alder reactions in natural product synthesis [31]. Interestingly, also photochemical [4+2] cycloadditions benefit from aqueous media [32]. The rate of the addition of singlet oxygen to an aromatic compound, for example, is significantly enhanced by water. Recently, the scaling up of water-based Diels–Alder reactions has been studied [33].

Lewis-acid catalysis of Diels–Alder reactions in water

There is a considerable potential for even further enhancing rates and selectivities of Diels–Alder reactions in water through the use of catalysts. In organic solvents Lewis-acid catalysis of Diels–Alder reactions is well established [34]. Unfortunately, extension of the use of Lewis-acid catalysts into aqueous media is hampered by the strong interactions between water and the catalyst as well as the Lewis-basic acceptor sites in the Diels–Alder reactants. However, once these difficulties are overcome, extreme rate enhancements are anticipated. The first example of such a Lewis-acid catalyzed Diels–Alder reaction has recently been published [35]. Efficient interactions between catalyst and substrate are achieved through bidentate coordination of the 3-phenyl-1-(2-pyridyl)-2-propen-1-one dienophile (**13**) to the aqua transition metal ion catalysts (entry 5 in Table 1). When comparing the rate of the catalyzed reaction in water with the uncatalyzed reaction in acetonitrile, accelerations amount up to 5 orders of magnitude. Also, the endo–exo ratio increases significantly in the presence of a Lewis-acid catalyst.

Interestingly, upon introduction of chiral α -amino acid-derived ligands enantioselectivity is induced [36]. For instance, in the presence of commercially available N^α -methyltryptophan the Cu^{2+} -catalyzed reaction of **13c** with cyclopentadiene gives the Diels–Alder adduct **14c** in 74% enantiomeric excess. This is the first example of enantioselectivity in a Lewis-acid catalyzed organic reaction in water. *Most significantly, water turned out to enhance the enantioselectivity as compared to organic solvents.* Mechanistic studies led to the conclusion that enantioselectivity in this reaction is a result of arene–arene interactions between the aromatic ring of the α -amino acid ligand and the pyridine ring of the dienophile, shielding one face of the dienophile from approach of the diene. It is not unlikely that water strengthens these arene–arene interactions, at least partly as a result of hydrophobic interactions. Since arene–arene interactions are held responsible for the enantioselectivity in many other reactions involving chiral catalysts, water seems to hold considerable potential as a solvent for enantioselective catalysis.

Micellar catalysis of Diels–Alder reactions [37]

In view of the hydrophobic character of most Diels–Alder reactants strong binding of these compounds to micellar aggregates is expected. In theory, the resulting concentration of the reactants in the micellar microenvironment is anticipated to promote the Diels–Alder reaction. Surprisingly, in practice, micelles are usually inhibiting Diels–Alder reactions, rather than promoting them [15,16,20,22,38]. Most likely, this is a result of the fact that in the cases studied so far the purely hydrocarbon diene prefers the interior of the micelles, whereas the more polar dienophile resides on average in the headgroup region of the aggregates. This spatial separation results in a modest inhibition of the reaction.

To date there is only one example of efficient micellar catalysis of a Diels–Alder reaction [39]. As compared to the uncatalyzed reaction in acetonitrile, micelles of copper didodecylsulfate turned out to be capable of inducing million-fold accelerations of the Diels–Alder reaction between **13** and cyclopentadiene. This large effect is mainly a result of the efficient interaction between the catalytically active copper ions and the dienophile. Both species are present in the headgroup region of the micelles in high local concentrations.

EPILOGUE

In this review we have highlighted that the use of water as a solvent for the Diels–Alder reaction is not merely an environmentally friendly alternative, but has considerable additional advantages in the form of significant water-induced increases in rates and selectivities. Possibilities exist for further rate enhancements and even for enantioselective catalysis by using (chiral) Lewis-acid catalysts in an aqueous medium. Despite these obvious benefits water is still not always the solvent of choice for the Diels–Alder reaction. The poor water solubility of many Diels–Alder reactants and the difficulties in achieving efficient interaction between Lewis-acid catalyst and substrate are major obstacles. The use of micelles and low concentrations of cosolvents might provide ways around these obstacles eventually transforming the Diels–Alder reaction into a clean and green process.

REFERENCES

1. (a) A. Lubineau, J. Auge, Y. Queneau. *Synthesis* 741 (1994). (b) C. Li. *Chem. Rev.* **93**, 2023 (1993). (c) J. B. F. N. Engberts, B. L. Feringa, E. Keller, S. Otto. *Recl. Trav. Chim., Pays-Bas* **115**, 457 (1996). (d) C. Li, T.-H. Chan. *Organic Reactions in Aqueous Media*. Wiley, New York (1997). (e) P. A. Grieco. *Organic Synthesis in Water*. Blacky Academic and Professional, London (1998).
2. O. Diels and K. Alder. *Ann.* **490**, 243 (1931).
3. R. B. Woodward and H. Baer. *J. Am. Chem. Soc.* **70**, 1161 (1948).
4. (a) H. Hopff and C. W. Rautenstrauch. *U.S. Patent* 2,262,002 (1942). (b) L. C. Lane and C. H. J. Parker. *U.S. Patent* 2,444,263 (1948).
5. T. A. Eggelte, H. De Koning, H. O. Huisman. *Tetrahedron* **29**, 2491 (1973).
6. R. Breslow and D. Rideout. *J. Am. Chem. Soc.* **102**, 7816 (1980).
7. (a) S. Otto, W. Blokzijl, J. B. F. N. Engberts. *J. Org. Chem.* **59**, 5372 (1994). (b) J. B. F. N. Engberts. *Pure Appl. Chem.* **67**, 823 (1995).
8. A likely explanation for some reactions: (a) P. A. Grieco, P. Garner, H. Zhen-Min. *Tetrahedron Lett.* **24**, 1897 (1983). But unlikely for others: (b) D. D. Sternbach and D. M. Rossana. *J. Am. Chem. Soc.*, **104**, 5853 (1982). (c) T. Dunams, W. Hoekstra, M. Pentaleri, D. Liotta. *Tetrahedron Lett.* **29**, 3745 (1988). (d) C. K. Pai and M. B. Smith. *J. Org. Chem.* **60**, 3731 (1995).
9. W. Blokzijl. *Ph.D. Thesis*, University of Groningen (1991).
10. Diels–Alder reactions of type A are governed by LUMO_{solvent}–HOMO_{solute} interactions. See: G. Desimoni, G. Faita, P. P. Righetti, L. Toma. *Tetrahedron* **46**, 7951 (1990).
11. (a) P. A. Grieco, J. J. Nunnes, M. D. Gaul. *J. Am. Chem. Soc.* **112**, 4549 (1990). (b) A. Lubineau and Y. Queneau. *J. Org. Chem.* **52**, 1001 (1987). (c) A. Kumar. *J. Org. Chem.* **59**, 230 (1994).
12. J. J. Gajewski. *J. Org. Chem.* **57**, 5500 (1992).
13. (a) W. Blokzijl, M. J. Blandamer, J. B. F. N. Engberts. *J. Am. Chem. Soc.* **113**, 4241 (1991). (b) W. Blokzijl and J. B. F. N. Engberts, *J. Am. Chem. Soc.* **114**, 5440 (1992).
14. See: (a) C. Cativiela, J. I. García, J. A. Mayoral, A. J. Royo, X. Assfeld, M. F. Ruiz-Lopez. *J. Phys. Org. Chem.* **5**, 230 (1992). (b) X. Assfeld, M. F. Ruiz-López, J. I. García, J. A. Mayoral, L. Salvatella. *J. Chem. Soc., Chem. Commun.* 1371 (1995). (c) C. Cativiela, J. I. Garcia, J. Gil, R.

- M. Martinez, J. A. Mayoral, L. Salvatella, J. S. Urieta, A. M. Mainar, M. H. Abraham. *J. Chem. Soc., Perkin Trans. 2* 653 (1997) and references therein.
15. G. K. Van der Wel, J. W. Wijnen, J. B. F. N. Engberts. *J. Org. Chem.* **61**, 9001 (1996).
 16. J. W. Wijnen and J. B. F. N. Engberts. *Liebigs Ann. / Recueil* 1085 (1997).
 17. A. Meijer, S. Otto, J. B. F. N. Engberts. *J. Org. Chem.* **63**, 8989 (1998).
 18. (a) J. F. Blake and W. L. Jorgensen. *J. Am. Chem. Soc.* **113**, 7430 (1991). (b) J. F. Blake, L. Dongchul, W. L. Jorgensen. *J. Org. Chem.* **59**, 803 (1994).
 19. T. R. Furlani and J. Gao. *J. Org. Chem.* **61**, 5492 (1996).
 20. I. Hunt and C. D. Johnson. *J. Chem. Soc., Perkin Trans. 2* 1051 (1991).
 21. A. Lubineau, H. Bienaymé, Y. Queneau, M. Scherrmann. *New J. Chem.* **18**, 279 (1994).
 22. (a) R. Breslow, U. Maitra, D. Rideout. *Tetrahedron Lett.* **24**, 1901 (1983). (b) R. Breslow and U. Maitra. *Tetrahedron Lett.* **25**, 1239 (1984).
 23. T. Asano and W. J. LeNoble. *Chem. Rev.* **78**, 407 (1978).
 24. J. A. Berson, Z. Hamlet, W. A. Mueller. *J. Am. Chem. Soc.* **84**, 297 (1962).
 25. C. Cativiela, J. I. García, J. A. Mayoral, L. Salvatella. *J. Chem. Soc., Perkin Trans. 2*, 847 (1994).
 26. I. Schlachter, Y. Mattay, J. Suer, U. Howeler, G. Wurthwein, E. Wurthwein. *Tetrahedron* **53**, 119 (1997).
 27. (a) A. Lubineau, J. Auge, N. Lubin. *J. Chem. Soc., Perkin Trans. 1* 3011 (1990). (b) S. Arseniyadis, R. Rodriguez, D. V. Yashunsky, J. Camera, G. Ourisson. *Tetrahedron Lett.* **35**, 4843 (1994).
 28. (a) P. A. Grieco, P. Garner, H. Zhen-Min. *Tetrahedron Lett.* **24**, 1897 (1983). (b) P. A. Grieco, K. Yoshida, P. Garner. *J. Org. Chem.* **48**, 3137 (1983). (c) P. A. Grieco, K. Yoshida, H. Zhen-Min. *Tetrahedron Lett.* **25**, 5715 (1984). (d) K. Yoshida, P. A. Grieco. *Chem. Lett.* 155 (1985). (e) P. A. Grieco, P. Galatsis, R. F. Spohn. *Tetrahedron* **42**, 2847 (1986). (e) K. Yoshida and P. A. Grieco. *J. Org. Chem.* **49**, 5257 (1984). (f) P. A. Grieco and M. D. Kaufman. *J. Org. Chem.* **64**, 6041 (1999) and references therein.
 29. (a) A. Lubineau and Y. Queneau. *Tetrahedron Lett.* **26**, 2653 (1985). (b) A. Lubineau and Y. Queneau. *Tetrahedron* **45**, 6697 (1989). (c) A. Lubineau, H. Bienayme, Y. Queneau. *Carbohydrate Res.* **270**, 163 (1995). (d) A. Lubineau, E. Grand, M.-C. Scherrmann. *Carbohydrate Res.* **297**, 169 (1997). (e) A. Lubineau, J. Auge, N. Lubin. *Tetrahedron Lett.* **32**, 7529 (1991). (f) A. Lubineau, J. Augé, E. Grand, N. Lubin. *Tetrahedron* **34**, 10265 (1994).
 30. H. Waldmann and M. Dräger. *Liebigs Ann.* 681 (1990).
 31. (a) M. Naruse, S. Aoyagi, C. Kibayashi. *Tetrahedron Lett.* **35**, 595 (1994). (b) M. Naruse, S. Aoyagi, C. Kibayashi. *J. Org. Chem.* **59**, 1358 (1994). (c) M. Naruse, S. Aoyagi, C. Kibayashi. *J. Chem. Soc., Perkin Trans. 1* 1113 (1996). (d) D. R. Williams, R. D. Gaston, I. B. Horton. *Tetrahedron Lett.* **26**, 1391 (1985). (e) L. Van Royen, R. Mijngheer, P. J. De Clercq. *Tetrahedron* **41**, 4667 (1985). (f) A. K. Saskena, V. M. Girijavallabhan, Y. Chen, E. Jao, R. E. Pike, J. A. Desai, D. Rane, A. K. Ganguly. *Heterocycles* **35**, 129 (1993).
 32. B. Cazin, J. Aubry, J. Rigaudy. *J. Chem. Soc., Chem. Commun.* 952 (1986).
 33. (a) G. Chen. *Diss. Abstr. Int.* **57**, 6934-B (1997). (b) W. Siegel and A. Kramer. *Eur. Pat. Appl.* EP 98-122148 981125.
 34. (a) H. B. Kagan and O. Riant. *Chem. Rev.* **92**, 1007 (1992). (b) U. Pindur, G. Lutz, C. Otto. *Chem. Rev.* **93**, 741 (1993).
 35. (a) S. Otto, J. B. F. N. Engberts. *Tetrahedron Lett.* **36**, 2645 (1995). (b) S. Otto, F. Bertocin, J. B. F. N. Engberts. *J. Am. Chem. Soc.* **118**, 7702 (1996).
 36. (a) S. Otto, G. Boccaletti, J. B. F. N. Engberts. *J. Am. Chem. Soc.* **120**, 4238 (1998). (b) S. Otto and J. B. F. N. Engberts. *J. Am. Chem. Soc.* **121**, 6798 (1999).
 37. A review on this topic is forthcoming: S. Otto and J. B. F. N. Engberts *Reactions and Synthesis in*

- Surfactant Systems*, J. Texter (Ed.), Marcel Dekker, New York, to be published.
38. (a) N. K. Sangwan and H.-J. Schneider. *J. Chem. Soc., Perkin Trans. II* 1223 (1989). (b) D. D. Sternbach and D. M. Rossana. *J. Am. Chem. Soc.* **104**, 5853 (1982). (c) J. W. Wijnen and J. B. F. N. Engberts. *J. Org. Chem.* **62**, 2039 (1997).
39. S. Otto, J. C. T. Kwak, J. B. F. N. Engberts. *J. Am. Chem. Soc.* **120**, 9517 (1998).